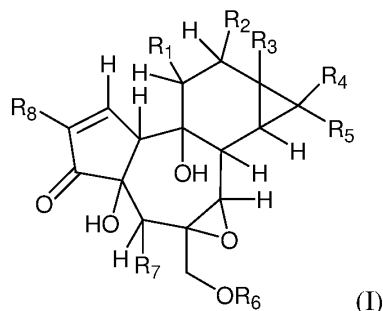


Claims

1. A method of dispersing a biofilm comprising Gram-negative bacteria comprising exposing the biofilm to an epoxytiglenone compound for formula (I):



5 wherein

R₁ is selected from hydrogen and C₁₋₆alkyl;

R₂ is selected from -OC₁₋₈alkyl, -OC₂₋₈alkenyl, -OC₂₋₈alkynyl, -OC(O)C₁₋₇alkyl, -OC(O)C₂₋₇alkenyl and -OC(O)C₂₋₇alkynyl;

10 R₃ is selected from -OH, -OC₁₋₈alkyl, -OC₂₋₈alkenyl, -OC₂₋₈alkynyl, -OC(O)C₁₋₇alkyl, -OC(O)C₂₋₇alkenyl and -OC(O)C₂₋₇alkynyl;

R₄ and R₅ are independently selected from hydrogen and C₁₋₆alkyl;

R₆ is selected from hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C(O)C₁₋₆alkyl, -C(O)C₂₋₆alkenyl, -C(O)C₂₋₆alkynyl, -C(O)C₃₋₈cycloalkyl, -C(O)C₁₋₆alkylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkenylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkynylC₃₋₈cycloalkyl, -C(O)aryl, -C(O)C₁₋₆alkylaryl, -C(O)C₂₋₆alkenylaryl and -OC(O)C₂₋₆alkynylaryl;

15 R₇ is selected from hydroxy, -OC₁₋₆alkyl, -OC₂₋₆alkenyl, -OC₂₋₆alkynyl, -OC(O)C₁₋₆alkyl, -OC(O)C₂₋₆alkenyl, -OC(O)C₂₋₆alkynyl, -C(O)C₃₋₈cycloalkyl, -C(O)C₁₋₆alkylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkenylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkynylC₃₋₈cycloalkyl, -OC(O)aryl, -OC(O)C₁₋₆alkylaryl, -C(O)C₂₋₆alkenylaryl and -C(O)C₂₋₆alkynylaryl;

20 R₈ is selected from hydrogen or C₁₋₆alkyl; or a salt thereof.

2. The method according to claim 1 wherein R₁ is C₁₋₃ alkyl.

3. The method according to either one of claims 1 or 2 wherein R₂ is selected from -OC(O)C₁₋₇alkyl, -OC(O)C₂₋₇alkenyl and -OC(O)C₂₋₇alkynyl.

4. The method according to claim 3 wherein R₂ is selected from -OC(O)C₃₋₆alkyl and -OC(O)C₃₋₆alkenyl.

25

5. The method according to any one of claims 1 to 4 wherein R₃ is selected from -OC(O)C₁₋₇alkyl, -OC(O)C₂₋₇alkenyl and -OC(O)C₂₋₇alkynyl.
6. The method according to claim 5 wherein R₃ is selected from -OC(O)C₃₋₆alkyl, -OC(O)C₃₋₆alkenyl and -OC(O)C₃₋₆alkynyl.
- 5 7. The method according to any one of claims 1 to 6 wherein R₄ and R₅ are each methyl.
8. The method according to any one of claims 1 to 7 wherein R₆ is selected from hydrogen, -C(O)C₁₋₆alkyl, -C(O)C₂₋₆alkenyl, -C(O)C₂₋₆alkynyl and -C(O)aryl.
9. The method according to claim 8 wherein R₆ is selected from hydrogen,
10 -C(O)CH₃, -C(O)CH₂CH₃, -C(O)CH(CH₃)₂ or -C(O)CH₂CH₂CH₃.
10. The method according to any one of claims 1 to 9 wherein R₇ is hydroxyl, -OC(O)C₁₋₆alkyl, -OC(O)C₂₋₆alkenyl or -OC(O)C₂₋₆alkynyl.
11. The method according to any one of claims 1 to 10 wherein R₈ is C₁₋₃alkyl.
12. The method according to any one of claims 1 to 11 wherein the alkyl or
15 alkenyl group of R₂ and/or R₃ are branched alkyl or alkenyl groups.
13. The method according to any one of claims 1 to 11 wherein the alkyl or alkenyl group of R₂ and/or R₃ are linear alkyl or alkenyl groups.
14. The method according to claim 1 wherein the compound of formula (I) is selected from:
 - 20 12-tigloyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 1);
 - 12,13-di-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 2);
 - 12-hexanoyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-
25 tiglien-3-one (Compound 3);
 - 12,13-dihexanoyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 4);
 - 12-tigloyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13-pentahydroxy-20-acetyloxy-1-tiglien-3-one (Compound 5);

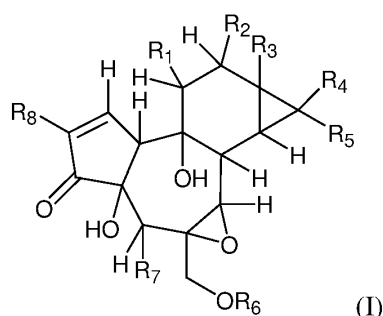
- 12-propanoyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 6);
- 12,13-ditigloyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 7);
- 5 12-(2-methylbutanoyl)-13-tigloyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 8);
- 12-butanoyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 9);
- 12-(3,3-dimethylbut-2-enoyl)-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 10);
- 10 12-hex-2,4-dienoyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 11);
- 12-tigloyl-13-(2-methylpropanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 12);
- 15 12-but-2-enoyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 13);
- 12-tigloyl-13-butanoyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 14);
- 12,13-dibutanoyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 15);
- 20 12,13-dipentanoyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 16);
- 12,13-di-(2*E*,4*E*)-hexa-2,4-dienoyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 17);
- 25 12,13-di-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one (Compound 18);
- 12-(2-methylprop-2-enoyl)-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one (Compound 19);
- 12,13-di-heptanoyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one (Compound 20); and
- 30 12,13-di-(3-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one (Compound 21);

or a salt thereof.

15. The method according to any one of claims 1 to 14 wherein the biofilm comprising Gram-negative bacteria comprises at least one Gram-negative bacteria selected from *Pseudomonas* species, *Acinetobacter* species, *Aeromonas* species,
 5 *Bacteroides* species, *Bordetella* species, *Borrelia* species, *Burkholderia* species, *Citrobacter* species, *Compylobacter* species, *Escherichia* species, *Enterobacter* species, *Flavobacterium* species, *Fusobacterium* species, *Klebsiella* species, *Leptospira* species, *Neisseria* species, *Helicobacter* species, *Hemophilus* species, *Legionella* species, *Moraxella* species, *Yersinia* species, *Oligella* species, *Pantoea* Species, *Porphyromonas*
 10 species, *Prevotella* species, *Proteus* species, *Raoutella* species, *Salmonella* species, *Serratia* species, *Shigella* species, *Sphingomonas* species, *Stenotrophomonas* species, *Treponema* species, *Veillonella* species and *Vibrio* species.

16. The method according to claim 15 wherein the Gram-negative bacteria is selected from *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*,
 15 *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Hemophilus influenzae*, *Legionella pneumophila*, *Yersinia pestis*, *Yersinia enterocolitica*, *Salmonella enterica*, *Salmonella bongori*, *Proteus mirabilis*, *Enterobacter cloacae*, *Serratia marcescens*, *Bacteroides fragilis*, *Fusobacterium necrophorum*, *Burkholderia cepacia* and *Prevotella intermedia*.

20 17. A method of treating a bacterial infection comprising a biofilm comprising Gram-negative bacteria, said method comprising locally administering to the bacterial infection an epoxytiglenone compound of formula (I):



(I)

wherein

- 45 -

R₁ is selected from hydrogen and C₁₋₆alkyl;

R₂ is selected from -OC₁₋₈alkyl, -OC₂₋₈alkenyl, -OC₂₋₈alkynyl, -OC(O)C₁₋₇alkyl, -OC(O)C₂₋₇alkenyl and -OC(O)C₂₋₇alkynyl;

R₃ is selected from -OH, -OC₁₋₈alkyl, -OC₂₋₈alkenyl, -OC₂₋₈alkynyl, -OC(O)C₁₋₇alkyl, -OC(O)C₂₋₇alkenyl and -OC(O)C₂₋₇alkynyl;

R₄ and R₅ are independently selected from hydrogen and C₁₋₆alkyl;

R₆ is selected from hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C(O)C₁₋₆alkyl, -C(O)C₂₋₆alkenyl, -C(O)C₂₋₆alkynyl, -C(O)C₃₋₈cycloalkyl, -C(O)C₁₋₆alkylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkenylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkynylC₃₋₈cycloalkyl, -C(O)aryl, -C(O)C₁₋₆alkylaryl, -C(O)C₂₋₆alkenylaryl and -OC(O)C₂₋₆alkynylaryl;

R₇ is selected from hydroxy, -OC₁₋₆alkyl, -OC₂₋₆alkenyl, -OC₂₋₆alkynyl, -OC(O)C₁₋₆alkyl, -OC(O)C₂₋₆alkenyl, -OC(O)C₂₋₆alkynyl, -C(O)C₃₋₈cycloalkyl, -C(O)C₁₋₆alkylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkenylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkynylC₃₋₈cycloalkyl, -OC(O)aryl, -OC(O)C₁₋₆alkylaryl, -C(O)C₂₋₆alkenylaryl and -C(O)C₂₋₆alkynylaryl;

R₈ is selected from hydrogen and C₁₋₆alkyl; or a pharmaceutically acceptable salt thereof.

18. The method according to claim 17 wherein the local administration is topical administration.

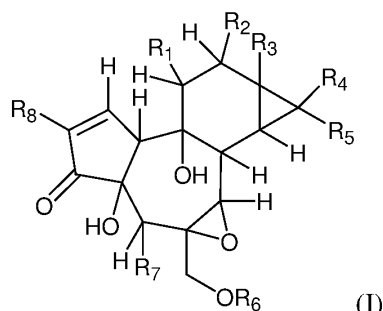
19. The method according to claim 17 or claim 18 wherein the infection is a post-surgical infection or an infection at the site of insertion of a medical device or implantation of an implant.

20. The method according to any one of claims 17 to 19 wherein the bacterial infection is a chronic infection.

21. The method according to any one of claims 17 to 20 wherein the administration is in combination with an antibiotic to which the Gram-negative bacteria is susceptible when in planktonic state.

22. A method of preventing a biofilm comprising Gram-negative bacteria forming on a medical device or dispersing a biofilm comprising Gram-negative bacteria on a medical device, said method comprising applying an epoxytiglicienone compound of formula (I) to the medical device: the compound of formula (I) comprising

- 46 -



(I)

wherein

R₁ is selected from hydrogen and C₁₋₆alkyl;

R₂ is selected from -OC₁₋₈alkyl, -OC₂₋₈alkenyl, -OC₂₋₈alkynyl, -OC(O)C₁₋₇alkyl, -
 5 OC(O)C₂₋₇alkenyl and -OC(O)C₂₋₇alkynyl;

R₃ is selected from -OH, -OC₁₋₈alkyl, -OC₂₋₈alkenyl, -OC₂₋₈alkynyl, -OC(O)C₁₋₇alkyl, -
 OC(O)C₂₋₇alkenyl and -OC(O)C₂₋₇alkynyl;

R₄ and R₅ are independently selected from hydrogen and C₁₋₆alkyl;

R₆ is selected from hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C(O)C₁₋₆alkyl,
 10 -C(O)C₂₋₆alkenyl, -C(O)C₂₋₆alkynyl, -C(O)C₃₋₈cycloalkyl, -C(O)C₁₋₆alkylC₃₋₈
 cycloalkyl, -C(O)C₂₋₆alkenylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkynylC₃₋₈cycloalkyl,
 -C(O)aryl, -C(O)C₁₋₆alkylaryl, -C(O)C₂₋₆alkenylaryl and -OC(O)C₂₋₆alkynylaryl;

R₇ is selected from hydroxy, -OC₁₋₆alkyl, -OC₂₋₆alkenyl, -OC₂₋₆alkynyl, -OC(O)C₁₋₆
 15 alkyl, -OC(O)C₂₋₆alkenyl, -OC(O)C₂₋₆alkynyl, -C(O)C₃₋₈cycloalkyl, -C(O)C₁₋₆alkylC₃₋₈
 cycloalkyl, -C(O)C₂₋₆alkenylC₃₋₈cycloalkyl, -C(O)C₂₋₆alkynylC₃₋₈cycloalkyl,
 -OC(O)aryl, -OC(O)C₁₋₆alkylaryl, -C(O)C₂₋₆alkenylaryl and -C(O)C₂₋₆alkynylaryl;

R₈ is selected from hydrogen and C₁₋₆alkyl; or a pharmaceutically acceptable salt thereof.

23. A method according to claim 22 wherein the medical device is a surgical
 20 instrument, catheter or medical implant.

24. A method according to either one of claims 22 and 23 wherein the medical device is a catheter.

25. A method according to claim 23 wherein the medical device is a dental implant.